FORM PTO-1390 (REV 5-93)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY DOCKET NO. 100564-00102
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		DATE: February 26, 2002
		U.S. APPLN. NO. (IF KNOWN, SEE 37 C.F.R. 1.5) New 10/049650

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/08280 ✓	24 August 2000 ✓	26 August 1999

TITLE OF INVENTION: METHOD FOR TRAINING A NEURAL NETWORK

APPLICANT(S) FOR DO/EO/US: Ronald KATES; Nadia HARBECK; Manfred SCHMITT

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371. (THE BASIC FILING FEE IS ATTACHED)

2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. ☒ This express request to begin national examination procedures [35 U.S.C. 371(f)] at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. ☐ A proper demand for International Preliminary Amendment was made by the 19th month from the earliest claimed priority date.

5. ☒ A copy of the International Application as filed [35 U.S.C. 371(c)(2)]
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).

6. ☒ A translation of the International Application into English [35 U.S.C. 371(c)(2)].

7. ☒ Amendments to the claims of the International Application under PCT Article 19 [35 U.S.C. 371(c)(3)]
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.

8. ☐ A translation of the amendments to the claims under PCT Article 19 [35 U.S.C. 371(c)(3)].

9. ☐ An oath or declaration of the inventor(s) [35 U.S.C. 371(c)(4)].

10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 [35 U.S.C. 371(c)(5)].

Items 11 - 16 below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98.

12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.

13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.

14. ☐ A substitute specification.

15. ☐ A change of power of attorney and/or address letter.

16. ☒ Other items or information: Drawing (Fig. 1; 1sheet)

U.S. APPLN. NO. (IF KNOWN SEE 37 C.F.R. 1.5) 10/04965	INTERNATIONAL APPLICATION NO. PCT/EP00/08280	ATTORNEY DOCKET NO. 100564-00102 DATE: February 26, 2002

17. ☐ The following fees are submitted:

Basic National Fee [37 C.F.R. 1.492(a)(1)-(5)]:

Search Report has been prepared by the EPO or JPO.....$890.00
International preliminary examination fee paid to USPTO (37 C.F.R. 1.482).....$710.00
No international preliminary examination fee paid to USPTO (37 C.F.R. 1.482) but international search fee paid to USPTO [37 C.F.R. 1.445(a)(2)].....$740.00
Neither international preliminary examination fee (37 C.F.R. 1.482) or international search fee [37 C.F.R. 1.445(a)(2)] paid to USPTO.....$1,040.00
International preliminary examination fee paid to USPTO (37 C.F.R. 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....$ 100.00

CALCULATIONS	PTO USE ONLY

ENTER APPROPRIATE BASIC FEE AMOUNT =				$ 890	
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date [37 C.F.R. 1.492(e)].				$	
Claims	Number Filed	Number Extra	Rate		
Total Claims	11 - 20 =	0	X $ 18.00	$	
Independent Claims	1 - 3 =	0	X $ 84.00	$	
Multiple dependent claim(s) (if applicable)			+ $280.00	$	
TOTAL OF ABOVE CALCULATIONS =				$ 890	
Reduction by one-half for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 C.F.R. 1.9, 1.27, 1.28).				$ 445	
SUBTOTAL =				$ 445	
Processing fee of $130.00 for furnishing the English translation later the ☐ 20 ☐ 30 months from the earliest claimed priority date [37 C.F.R. 1.492(f)]. +				$	
TOTAL NATIONAL FEE =				$ 445	
Fee for recording the enclosed assignment [37 C.F.R. 1.21(h)]. The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. 3.28, 3.31). $40.00 per property +				$	
TOTAL FEES ENCLOSED =				$ 445	
				Amount to be refunded	$
				Charged	$

a. ☒ A check in the amount of $445 to cover the above fees is enclosed.
b. ☐ Please charge my Deposit Account No. 01-2300 in the amount of $ to cover the above fee. A duplicate copy of this sheet is enclosed.
c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 01-2300.

NOTE: Where an appropriate time limit under 37 C.F.R. 1.494 or 1.495 has not been met, a petition to revive [37 C.F.R. 1.137(a) or (b)] must be filed and granted to restore the application to pending status.

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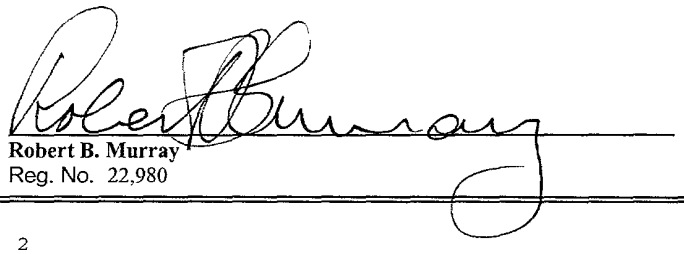

Robert B. Murray
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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:
KATES et al.

Appln. No.: PCT/EP00/08280

Filed: Concurrently herewith Attorney Dkt. No.: 100564-00102

For: METHOD FOR TRAINING A NEURAL NETWORK

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231 February 26, 2002

Sir:

Prior to calculation of the filing fees and initial examination of the application, please amend the above-identified application as follows:

IN THE CLAIMS:

Please amend claims 3, 4, 6, 7, 10 & 11 as follows:

3. (Amended) The method as claimed in claim 1, characterized in that furthermore the value of the bias of the receiving neuron is adapted in step a3).

4. (Amended) A method for training a neural network in accordance with the preamble of claim 1 and if desired with the characterizing parts of claim 1, characterized in that the training of the neural network comprises a structure simplification procedure, that is to say the location and elimination of synapses that have no significant influence on the curve of the risk function in that

b1) one selects a synapse,

b)2 one assumes that said synapse does not have a significant influence on the curve of the risk function,

b)3 one interrupts said synapse,

b4) one compares the reaction of the neural network changed in accordance with step b3) with the reaction of the unchanged neural network, and

b5) if the variation of the reaction does not exceed a predetermined level, one decided to keep the change made in step b3).

6. (Amended) The method as claimed in claim 1, characterized in that the value of a likelihood function is calculated for the neural network to represent the reaction of the neural network.

7. (Amended) The method as claimed in claim 1, characterized in that the structure variants of the neural network are compared using a significance test.

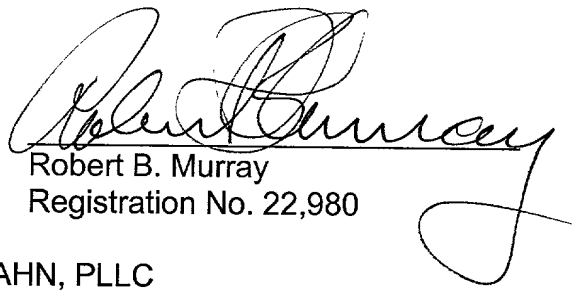
10. (Amended) The method as claimed in claim 1, characterized in that, to compare two structure variants of the neural network, the ratio of the values of the likelihood functions for said two structure variants is calculated.

11. (Amended) A method for training a neural network in accordance with the preamble of claim 1 and if desired with the characterizing parts of claim 1, characterized in that the training of the neural network comprises an optimization procedure in which the strengths of the individual synapses, that is to say the strengths of the connections between the neurons, are optimized, and in that the simplex method which is known per se is used for said optimization.

REMARKS

Claims 1-11 are pending in this application. By this Amendment, claims 3, 4, 6, 6, 10 & 11 are amended to correct the multiple dependency thereof and to place this application into better condition for examination. No new matter is added.

Respectfully submitted,



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a5) if the variation of the reaction does not exceed a predetermined level, one decides to keep the change made in step a3).

2. The method as claimed in claim 1, characterized in that the two sending neurons are located on one and the same layer.

3. The method as claimed in claim 1 [or 2] characterized in that furthermore the value of the bias of the receiving neuron is adapted in step a3).

4. A method for training a neural network in accordance with the preamble of claim 1 and if desired with the characterizing parts of [any of Claim 1 claims 1 to 3], characterized in that the training of the neural network comprises a structure simplification procedure, that is to say the location and elimination of synapses that have no significant influence on the curve of the risk function, in that

b1) one selects a synapse,

b2) one assumes that said synapse does not have a significant influence on the curve of the risk function,

b3) one interrupts said synapse,

b4) one compares the reaction of the neural network changed in accordance with step b3) with the reaction of the unchanged neural network, and

b5) if the variation of the reaction does not exceed a predetermined level, one decides to keep the change made in step b3).

5. The method as claimed in claim 4, characterized in that, when in the course of the structure simplification procedure n-1 synapses have already been eliminated and the strength of the influence of an nth synapse is being tested, the reaction of the neural network reduced by n synapses is not only compared with the reaction of a network reduced by only n-1 synapses, but also with the reaction of the neural network with its complete structure as present at the beginning of said structure simplification procedure, and in that the

elimination of the nth synapse is only retained if the deviation of the reaction does not exceed a predetermined level for both comparisons.

6. The method as claimed in [any claim 1 of claims 1 to 5], characterized in that the value of a likelihood function is calculated for the neural network to represent the reaction of the neural network.

7. The method as claimed in [any claim 1 of claims 1 to 6], characterized in that the structure variants of the neural network are compared using a significance test.

8. The method as claimed in claim 7, characterized in that the structure variants of the neural network are compared using the CHI-SQUARED test which is known per se.

9. The method as claimed in claim 7, characterized in that the structure variants of the neural network are compared using the BOOT-STRAPPING method which is known per se.

10. The method as claimed in [any claim 1 of claims 1 to 8], characterized in that, to compare two structure variants of the neural network, the ratio of the values of the likelihood functions for said two structure variants is calculated.

11. A method for training a neural network in accordance with the preamble of claim 1 and if desired with the characterizing parts of [any claim 1 of claims 1 to 10], characterized in that the training of the neural network comprises an optimization procedure in which the strengths of the individual synapses, that is to say the strengths of the connections between the neurons, are optimized, and in that the simplex method which is known per se is used for said optimization.

Method for training a neural network

Description

1. FIELD OF THE INVENTION

The invention relates to a method for training a neural network to determine risk functions for patients following a first occurrence of a predetermined disease on the basis of given training data records containing objectifiable and for the most part metrologically captured data relating to the medical condition of the patient, wherein the neural network comprises an input layer having a plurality of input neurons and at least one intermediate layer having a plurality of intermediate neurons, as well as an output layer having a plurality of output neurons, and a multiplicity of synapses which interconnect two neurons of different layers in each case.

2. TECHNICAL BACKGROUND - PRIOR ART

2.1. General

For large scale data analysis, neural networks have supplemented or replaced hitherto conventional methods of analysis in many fields. It has namely been shown that neural networks are better than conventional methods at discovering and identifying in the datasets hidden, not immediately evident dependencies between individual input data. When new data of the same data type is input, neural networks which have been trained using a known dataset therefore deliver more reliable results than previous methods of analysis.

In the field of medical applications for example, the use of neural networks to determine a survival function for patients suffering from a particular disease, such as cancer, is known. Said survival function

indicates the probability of a predetermined event occurring for the patient in question depending on the time that has elapsed since the first occurrence of the disease. Said predetermined event need not necessarily be the death of the patient, as would be inferred from the designation "survival function", but may be any event, for example a recurrence of cancer.

The data records comprise a whole range of objectifiable information, that is to say data on whose value any neural network operator has no influence and whose value can be automatically captured if desired. In the case of breast cancer this is information about the patient's personal data, such as age, sex and the like, information about the medical condition, such as number of lymph nodes affected by cancer, biological tumor factors such as upA (Urokinase Plasminogen Activator), its inhibitor PAI-1 and similar factors, as well as information about the treatment method, for example type, duration and intensity of chemotherapy or radiotherapy. It goes without saying that a whole range of the abovementioned information, in particular the information about the medical condition, can only be determined using suitable measuring apparatus. Furthermore, the personal data can be automatically read in from suitable data media, for example machine-readable identity cards or the like. If they are not all available at the same time, which is often the case especially with laboratory measurements, the objectifiable data can of course be temporarily stored in a database on a suitable storage medium before they are fed to the neural network as input data.

2.2. The neural network as signal filter

In accordance with the foregoing, therefore, it is possible to conceive of a neural network as a kind of "signal filter" that filters out a meaningful output signal from a noisy, and therefore as yet non-meaningful input signal. As with any filter, whether or how well the

filter is able to fulfill its function depends on whether it is possible to keep the intensity of the filter's intrinsic noise low enough that the signal to be filtered out is not lost in this intrinsic noise.

The greater the number of data records available for training the neural network on the one hand and the simpler the structure of the neural network on the other hand, the lower the intensity of the "intrinsic noise" of a neural network. Moreover, the generalizability of the network increases, the simpler the structure of the neural network. In the case of a conventional procedure in the prior art, therefore, one part of the training of neural networks is concerned with locating and eliminating parts of the structure that can be dispensed with for obtaining a meaningful output signal. With this "thinning out" (also known as "pruning" in the jargon) however, a further constraint to be taken into account is that the structure of the neural network cannot be "pruned" ad infinitum because as the complexity of the neural network is reduced, its ability to map complex interrelationships, and hence its meaningfulness, is also diminished.

2.3. Problems with medical application

In practice, and in particular in the case of the medical application of neural networks mentioned at the beginning, the problem is often encountered that only very small datasets of typically a few hundred data records are available for training the neural network. To compound the difficulty, not only a training dataset, but also a validation dataset and a generalization dataset must be provided for the training. The significance of said two datasets will be discussed in greater detail below in sections 5.5 and 5.7.

With such small datasets, the use of known pruning methods always led to so great a simplification of the structure of the neural network that the meaningfulness of the neural network diminished to an

unacceptable level. To nevertheless obtain neural networks that delivered meaningful output signals after completion of the training phase, in the prior art neural networks with a rigid, that is to say fixed and invariable, structure were used where only small training datasets were available. The degree of complexity, or the simplicity, of this rigid structure was selected here on the basis of empirical knowledge in such a way that the neural network had on the one hand a high degree of meaningfulness while on the other hand having a still acceptable intrinsic noise level. It has hitherto been assumed that the specification of an invariable structure was unavoidable.

Another problem with medical applications of neural networks is the fact that only "censored" data are available for training. The term "censored" is used to denote the circumstance that it is not possible to foresee the future development for patients who have fortunately not yet suffered a relapse at the time of data capture, and statements about the survival function are therefore only possible up until the time the data were recorded.

It goes without saying that in particular in the case of medical applications it is not possible to forego a truly meaningful result under any circumstances whatsoever. Under no circumstances is it namely acceptable for even one single patient to be denied a treatment simply because the neural network did not consider it necessary. The consequences for the patient could be incalculable.

With respect to the details of the prior art outlined above, please see the articles listed in section 6. "References".

3. OBJECT OF THE INVENTION

In the light of the above, the object of the invention is to provide an automatic method for training

a neural network to determine risk functions for patients following a first occurrence of a predetermined disease, which method permits, despite a low number of available training data records, the use of a neural network having a variable structure and the optimization of its structure in at least one structure simplification step.

4. ACHIEVEMENT OF THE OBJECT

According to the invention, this object is achieved by a method for training a neural network to determine risk functions for patients following a first occurrence of a predetermined disease on the basis of given training data records containing objectifiable and metrologically captured data relating to the medical condition of the patient, wherein the neural network comprises:

- an input layer having a plurality of input neurons,
- at least one intermediate layer having a plurality of intermediate neurons,
- an output layer having a plurality of output neurons, and
- a multiplicity of synapses which interconnect two neurons of different layers in each case,

wherein the training of the neural network comprises a structure simplification procedure, that is to say the location and elimination of synapses that have no significant influence on the curve of the risk function, in that one either

a1) selects two sending neurons that are connected to one and the same receiving neuron,

a2) assumes that the signals output from said sending neurons to the receiving neuron essentially exhibit the same qualitative behavior, that is to say are correlated to one another,

a3) interrupts the synapse of one of the two sending neurons to the receiving neuron and instead adapts accordingly the weight of the synapse of the

respective other sending neuron to the receiving neuron,

a4) compares the reaction of the neural network changed in accordance with step a3) with the reaction of the unchanged neural network, and

a5) if the variation of the reaction does not exceed a predetermined level, decides to keep the change made in step a3),

or in that one

b1) selects a synapse,

b2) assumes that said synapse does not have a significant influence on the curve of the risk function,

b3) interrupts said synapse,

b4) compares the reaction of the neural network changed in accordance with step b3) with the reaction of the unchanged neural network, and

b5) if the variation of the reaction does not exceed a predetermined level, decides to keep the change made in step b3).

A neural network trained in the manner described above assists the attending physician for example when deciding on the follow-up treatment for a particular newly operated patient. For this the physician can input into the neural network the patient data and the data metrologically captured in the laboratory relating to the medical condition of the first treatment, and receives from the neural network information about what type of follow-up treatment would produce the most favorable survival function for the patient in question. It is of course also possible to take account of the aggressiveness of the individual types of follow-up treatment so that, given an equally favorable or virtually equally favorable survival function, the least aggressive follow-up treatment for the patient can be selected.

5. EXEMPLARY EMBODIMENT

The invention is explained in greater detail below with reference to an exemplary embodiment.

5.1. Structure of neural networks

Fig. 1 shows the structure of a neural network which is constructed in the manner of a multi-layer perceptron. In this case the neural network comprises:

- an input layer having a plurality of input neurons N_i (i for "input neuron"),
- at least one intermediate layer having a plurality of intermediate neurons N_h (h for "hidden neuron"),
- an output layer having a plurality of output neurons N_o (o for "output neuron"), and
- a multiplicity of synapses which interconnect two neurons of different layers in each case.

In the simplified embodiment according to Fig. 1, on which the following discussion will be based for the sake of clarity, only a single intermediate layer is provided, and the neurons (or nodes as they are also frequently called) of the output layer are connected via synapses (also called "connectors") to both each neuron of the input layer and to each neuron of the intermediate layer.

The number of input neurons is usually chosen depending on the number of objectifiable items of information available. However, if the time required for determining the reaction of the neural network should consequently rise to an unacceptable level, then it is possible, for example with the aid of neural networks having a greatly simplified structure, to make a preliminary estimation of the significance of the individual objectifiable items of information for the meaningfulness of the overall system. It should however be stressed that this preliminary estimate is also performed automatically and without the intervention of the respective operator. Furthermore, the number of

output neurons is chosen to be large enough that, for the purposes of a series expansion of the survival function, a sufficient number of series expansion terms are available to achieve a meaningful approximation to the actual survival function. Finally, the number of intermediate neurons is chosen to be large enough that the results of the trained neural network are meaningful, but small enough that the time required to determine the result is acceptable.

5.2. Function of neural networks

5.2.1. General

Each neuron receives a stimulation signal S, processes it in accordance with a predetermined activation function F(S) and outputs a corresponding response signal A = F(S) which is fed to all neurons located below said neuron. The stimulation signal S_y that acts on the neuron N_y in question is usually formed by summing the response signals A_x of the neurons N_x located above said neuron N_y, with the contributions of the individual neurons N_x in each case being factored with a weighting factor w_{xy} that states the strength of the synapse connecting the two neurons into the sum.

Stimulation signal: $S_y = \sum_x w_{xy} \cdot A_x$

Response signal: $A_y = F(S_y)$

5.2.2. Input layer

The stimulation signals S_i of the input neurons N_i are formed by the input data $x_{i,j}$ relating to a particular patient j.

Stimulation signal: $S_i = x_{i,j}$

In order to be able to interpret the weights of the synapses of a neural network appropriately, it is

preferable to work with variables whose values are of the magnitude of 1. To achieve this despite the usually very different distributions of input data, it is customary to subject the input data to an appropriate transformation. Said transformation is performed by the activation function F_i of the input neurons:

Response signal: $A_i = \tanh[(S_i - S_{i,mean})/S_{i,Q}]$

For the input data $x_{i,j}$, therefore, firstly the mean value $S_{i,mean}$ of the patients j belonging to the training dataset is formed. Secondly a scaling factor $S_{i,Q}$ is formed. If the value of an input variable $x_{i,j}$ is above the mean $S_{i,mean}$, then scaling is performed in accordance with the 75% quartile. If, on the contrary, it is below the mean value, then scaling is performed in accordance with the 25% quartile. Finally, by using the hyperbolic tangent function as the activation function F_i, scaled response signals with values in the range between -1 and +1 are readily obtained.

Note that the above transformation can be omitted for input data that already exhibit the desired distribution, categorical values or binary values.

5.2.3. Intermediate layer

The stimulation signal S_h for the neurons N_h of the intermediate layer is formed by the weighted sum of the response signals A_i of all neurons N_i of the input layer:

Stimulation signal: $S_h = \sum_i w_{ih} \cdot A_i$

Said stimulation signal S_h is transformed by the neurons N_h in accordance with a given activation function F_h, which may again be the hyperbolic tangent function for example, into a response signal A_h:

Response signal: $A_h = F_h(S_h - b_h)$

In the field of neural networks, the parameters b_h are referred to as the "bias" of the respective neuron. Like the values of the synapse weights w_{xy}, the values of said bias parameters b_h are also determined during training of the neural network.

5.2.4. Output layer

The stimulation signal S_o and the response signal A_o for a neuron N_o of the output layer are determined analogously:

Stimulation signal: $S_o = \Sigma_i w_{io} \cdot (A_i - c_i) + \Sigma_h w_{ho} \cdot A_h$

Response signal: $A_o = F_o(S_o - b_o)$

The parameters b_o again indicate the "bias" of the neurons N_o of the output layer, while the parameters c_i serve to adapt the stimulation contributions of the neurons N_i of the input layer and N_h of the intermediate layer. The values of both the parameters b_o and the parameters c_i are determined during the training phase of the neural network. With respect to the bias values b_o, it may be favorable to require as a constraint that the response of all output neurons N_o averaged across the complete training dataset is zero. The identity function $F_o(x) = x$ can be used as the activation function F_o for most applications, in particular for the present case where the survival function is being determined for cancer patients.

The response signals A_o of the output neurons N_o indicate the respective coefficients of the associated terms of the series expansion of the survival function sought.

5.3. The survival function

As already mentioned above, the input data comprise information about the patient's personal data as well as information about the medical condition. All

these data are captured at a time t = 0, in the case of cancer patients the time of the first operation for example. Following the first operation, the patients then undergo a particular follow-up treatment, which may include chemotherapy and/or radiotherapy for example.

The survival function S(t) indicates for a patient in question at a time t the probability that a particular event has not yet occurred. Said particular event may be, for example, a recurrence of cancer, or also in the worst case the death of the patient. In any case, S(0) = 1 holds for the survival function. In addition, $S(\infty) = 1$ is usually assumed.

According to conventional notation, it is possible to define an event density f(t) and a risk function $\lambda(t)$ on the basis of the survival function S(t):

$$f(t) = -dS/dt$$

$$\lambda(t) = f(t)/S(t)$$

from which it follows that:

$$\lambda(t) = -(d/dt)[\ln S(t)]$$

If one knows the curve of the risk function $\lambda(t)$ therefore, it is possible to reconstruct the curve of the survival function S(t) by means of integration.

The task of the neural network is to model the curve of the risk function $\lambda(t)$ in the same way as a series expansion:

$$\lambda(t) = \lambda_0 \cdot \exp[\sum_o B_o(t) \cdot A_o]$$

According to the above notation, the parameters A_o denote the response signals of the neurons N_o of the output layer of the neural network. In the context of the present invention, λ_o is a parameter independent of t which is used as a scaling factor. $B_o(t)$ denotes a set of

functions that, as base functions of the series expansion, enable a good approximation to the actual curve of the risk function. It is possible to use for example the fractal polynomials or else functions such as t^p (where p is not necessarily an integer) as the function set $B_o(t)$. $B_{o1}(t) = 1$; $B_{o2}(t) = \text{const} \cdot t^{1/2}$, ... were used for the present invention.

5.4. Training of the neural network - preparations

5.4.1. The optimization function

The training dataset comprises the data records of a plurality of patients for whom not only personal data and information about the medical condition, but also information about the type of follow-up treatment and the further progress of the disease are known. From the collected data relating to the further progress of the disease, an "actual survival function" is constructed according to the following rules: if the predetermined event, for example a relapse or the death of the patient, has already occurred for a particular patient at a time t, then his contribution δ to the "actual survival function" is set to $\delta = 0$ before time t and to $\delta = 1$ at time t and after time t. Patients for whom the predetermined event has not yet occurred at the time the training dataset was created ("censored" data) contribute only $\delta = 0$ to the "actual survival function" at all times. During the training phase the weights w_{xy} of the synapses and the other optimization parameters set out in section 5.2. above are then set in such a way that the survival function delivered by the neural network optimally matches the "actual survival function".

This can be achieved, for example, by defining a suitable optimization function O for this purpose and searching for a local, in the most favorable case even the global, minimum of said optimization function in the space covered by the optimization parameters. To define the optimization function O, it is already known in the

prior art to start from a so-called likelihood function L:

$$O = -\ln L$$

According to the invention

$$L = \prod_j [f_j(t)]^{\delta} \cdot [S_j(t)]^{1-\delta}$$

is chosen to represent the likelihood function where, in accordance with the notation introduced in section 5.3., $f_j(t)$ and $S_j(t)$ denote the event density and the survival function for the patient j of the training set. Said likelihood function has the advantage that the computational effort rises only approximately proportionately to the number of patients included in the training dataset.

Another way of representing the likelihood function is:

$$L = \prod_j \langle \exp[\Box_o B_o(t) \cdot A_{oj}] \; \prod \Box_I \exp[\Box_1 B_o(t) \cdot A_{o1}] \rangle$$

where the product is formed across all patients j for whom the predetermined event has already occurred at time t, and where the first sum in the denominator of the quotient is formed across all patients l for whom the predetermined event has not yet occurred at time t.

The computational effort associated with this representation does however rise approximately proportionately to the square of the number of patients included in the training dataset.

5.4.2. The initialization

As is known per se in the prior art, to initialize the network optimization parameters, for example the weights of the synapses connecting the neurons, it is possible to assign stochastically to said parameters small values that conform to certain

normalization rules. It is additionally possible here to include in the normalization findings obtained in preliminary test runs on neural networks having a greatly simplified structure.

5.5. Training the neural network - simplex method

As is customary, the search for a local or the global minimum of the optimization function is performed in several steps or cycles. According to the invention, however, for the first time the simplex method proposed by Nelder and Mead (see section 6. "References") is used in a neural network for this search. A simplex is an (n+1)-dimensional structure in an n-dimensional space which surrounds the current basepoint in the n-dimensional space, i.e. a triangle in 2-dimensional space, a tetrahedron in a 3-dimensional space and so forth. In what directions and at what distances from the current basepoint the (n+1) vertices are arranged is determined here from the vertices of the preceding cycle on the basis of the characteristics of the optimization function.

This method leads to a strictly monotonic decreasing sequence of basepoints. It can be continued until either (within given precision limits) a local or global minimum has been identified or another termination criterion has been fulfilled. In connection with said further termination criterion, the abovementioned validation dataset now comes into play:

The abovementioned monotonic decrease in basepoints can arise on the one hand from actually objectifiable characteristics of the optimization function specified for the training dataset. On the other hand, it is also possible that the decrease occurs in the range of a valley of the optimization function caused by stochastic fluctuations. The latter effect however only simulates a learning success. For this reason, according to the invention the characteristics of the optimization function specified on the basis of the validation dataset

are also investigated at the same basepoints. If it is then determined that the basepoints of the "validation data optimization function" also exhibit a monotonic decrease, then it can be assumed that one is still in a "true" learning phase of the neural network. If on the other hand the sequence of basepoints of the "validation data optimization function" stagnates, or if it even rises again, it must be assumed that with respect to the "training data optimization function" one is in a valley caused by stochastic fluctuations which only simulates a learning progress. The cyclical execution of the simplex method can therefore be interrupted.

The main advantage of the simplex method is that it can be performed solely on the basis of the optimization function, and also that the step length and step direction can be automatically specified.

5.6. Training the neural network - structure simplification ("pruning")

Once the search for a local or the global minimum has been completed, the next training step is to investigate whether it is possible to simplify the structure of the neural network on the basis of the findings so far. This "pruning" is concerned with investigating which of the synapses have so little influence on the overall function of the neural network that they can be omitted. In the simplest case this can be, for example, permanently setting the weight assigned to them to zero. However, in principle it is equally conceivable to "freeze" the weight of the respective synapse to a fixed value. It is advantageous to alternate between simplex optimization steps and structure simplification steps in an iterative process. It would of course be desirable for the neural network to undergo a new simplex optimization after a single synapse has been excluded. In view of the total time required for training however, this is unjustifiable. In practice a favorable

compromise has proved to be the removal during a structure simplification step of at most 10% of the synapses still present at the beginning of said step.

According to the invention the two methods described below in sections 5.6.1. and 5.6.2. are used for structure simplification.

5.6.1. Likelihood method

With this method the value of the likelihood function is first calculated as a reference value on the basis of the complete structure of the neural network in its present state of training, i.e. using the current values of the weights of all synapses. Following this, the influence of a given synapse is suppressed, i.e. the value of the weight of this synapse is set to zero. The value of the likelihood function is then calculated for the thus simplified network structure, and the ratio of this value to the reference value is formed.

Once said likelihood ratio has been calculated for all synapses, when performing the steps described below, a start is made with the synapse for which the value of the likelihood ratio is nearest to one:

Assuming that the network structure has already been simplified by (x-1) synapses and the significance of the xth synapse is now being investigated, then the following three network structure variants are compared: firstly the complete structure of the neural network in its current state of training with all synapses still present prior to this structure simplification state, secondly the network structure excluding the (x-1) synapses already suppressed in this structure simplification step, and thirdly the network structure now also excluding the xth synapse. Following this, using a significance test the third structure variant is compared firstly with the first structure variant (complete structure) and secondly with the second structure variant ((x-1) synapses suppressed). If even just one of the two tests produces too great a deviation

from the third structure variant, then the respective synapse is retained at least for the next simplex optimization step.

The CHI-SQUARED test (cf. section 6. "References", Document .....) which is known per se can be used as a significance test for example. Alternatively, said significance test could also be performed using the BOOT-STRAPPING method (cf. section 6. "References", Document .....) which is likewise known per se. The use of the CHI-SQUARED test is particularly favorable if the reaction of the neural network is determined on the basis of a likelihood function. The BOOT-STRAPPING method is also suitable with other types of functions for representing the reaction of the neural network.

5.6.2. Correlation method

The exclusion or suppression of synapses according to the correlation method is based on the consideration that it could be possible for two neurons located on one and the same layer to have qualitatively the same influence on one neuron on a lower layer. In this case the reaction of the neural network, or to be more precise the response signal of said latter neuron, should not change significantly if said neuron is stimulated by only one of the two neurons located above it, and the influence of the second neuron is taken into account by strengthening the remaining synapse. It would then be possible to omit the synapse leading from the second neuron to the neuron in question.

a. Synapses connecting input neurons and output neurons

In accordance with section 5.2.4., the contribution of the response signal of two input neurons to the stimulation signal of an output neuron takes the form:

$$S_o = w_{1o} \cdot (A_1 - c_1) + w_{2o} \cdot (A_2 - c_2)$$

If one then assumes that the two response signals A_1 and A_2 are correlated at least approximately to one another in accordance with

$$A_2 = m \cdot A_1 + n$$

and that the weight w_{1o} is greater than the weight w_{2o}, then the following holds for the stimulation signal S_o:

$$S_o = (w_{1o} + w_{2o} \cdot m) \cdot A_1 + (n \cdot w_{2o} - w_{1o} \cdot c_1 - w_{2o} \cdot c_2)$$

$$= w^*_{1o} \cdot (A_1 - c^*_1)$$

where

$$w^*_{1o} = w_{1o} + w_{2o} \cdot m$$

and

$$c^*_1 = -[(n \cdot w_{2o} - w_{1o} \cdot c_1 - w_{2o} \cdot c_2)] / (w_{1o} + w_{2o} \cdot m)$$

If w^*_{1o} is non-small, the behavior of the neural network can be tested with the following assumptions:

1. Replace the weight w_{1o} by w^*_{1o};
2. Replace the parameter c_1 by c^*_1; and
3. Suppress the synapse from the input neuron N_2 to the output neuron N_o.

If the outcome of this test, which can again be performed as a CHI-SQUARED test for example, is positive, then it is possible to omit the synapse from the input neuron N_2 to the output neuron N_o.

b. Synapses connecting input neurons and intermediate neurons

The contribution of the response signal of two input neurons to the stimulation signal of an intermediate neuron can also be treated analogously, in

which case it is advisable, for reasons that will become immediately apparent below, to treat the stimulation signal of the intermediate neuron including its "bias":

$$S_h - b_h = w_{1h} \cdot A_1 + w_{2h} \cdot A_2$$

If one again assumes that the two response signals A_1 and A_2 are correlated at least approximately to one another in accordance with

$$A_2 = m \cdot A_1 + n$$

and that the weight w_{1h} is greater than the weight w_{2h}, then the following holds for the stimulation signal S_h:

$$S_h - b_h = (w_{1h} + w_{2h} \cdot m) \cdot A_1 + n \cdot w_{2h}$$

or

$$S_h - b^*_h = w^*_{1h} \cdot A_1$$

where

$$w^*_{1h} = w_{1h} + w_{2h} \cdot m$$

and

$$b^*_h = b_h + n \cdot w_{2h}$$

If w^*_{1h} is non-small, the behavior of the neural network can be tested with the following assumptions:

1. Replace the weight w_{1h} by w^*_{1h};
2. Replace the bias b_h by b^*_h; and
3. Suppress the synapse from the input neuron N_2 to the intermediate neuron N_h.

If the outcome of this test, which can again be performed as a CHI-SQUARED test for example, is positive, then it is possible to omit the synapse from the input neuron N_2 to the intermediate neuron N_h.

c. Synapses connecting intermediate neurons and output neurons

Synapses leading from intermediate neurons to output neurons can also be treated analogously. With respect to the bias values b_o, however, the further constraint mentioned in section 5.2.4. may need to be taken into account.

5.6.3. Testing the topology

The above-described pruning of the structure of the neural network can result in individual neurons no longer being connected to any other neurons. This is the case for example if an input neuron is not connected to any intermediate neuron nor to any output neuron, or if an output neuron is not connected to any intermediate neuron nor to any input neuron. It is therefore only logical to completely deactivate these neurons that no longer have an influence on the function of the neural network.

Intermediate neurons that are still connected to neurons on the input layer but not to neurons on the output layer constitute a special case. Said intermediate neurons can no longer exert any influence on the function of the neural network. The synapses leading from the input layer to these intermediate neurons can therefore also be suppressed, i.e. the weights of said synapses can be set to zero.

The converse case can however also occur, namely that an intermediate neuron is still connected to the output layer, but no longer has any connection to the input layer. At best said intermediate neurons can output to the output neurons a response signal that is dependent on their "bias". However, a signal of this type has no information content whatsoever that would be significant for the function of the neural network. It is therefore also possible to suppress the remaining synapses of said intermediate neurons.

5.7. Generalization

On completion of the training phase it is necessary to test the performance of the trained neural network to obtain a measure of how meaningful the survival functions delivered by this neural network actually are. The abovementioned generalization dataset, which had no influence whatsoever on the training of the neural network and thus enables objective results, is used for this purpose.

5.8. Concluding remarks

In conclusion it should be mentioned that, in addition to the tumor-specific factors upA and PAI-1 explicitly mentioned above which allow statements to be made about invasion, it is also possible to take further such factors into account. Among others, these include factors for proliferation, for example the S phase and Ki-67, and other processes that influence tumor growth.

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Claims

1. A method for training a neural network to determine risk functions for patients following a first occurrence of a predetermined disease on the basis of given training data records containing objectifiable and metrologically captured data relating to the medical condition of the patient, wherein the neural network comprises:

- an input layer having a plurality of input neurons,
- at least one intermediate layer having a plurality of intermediate neurons,
- an output layer having a plurality of output neurons, and
- a multiplicity of synapses which interconnect two neurons of different layers in each case,

characterized in that the training of the neural network comprises a structure simplification procedure, that is to say the location and elimination of synapses that have no significant influence on the curve of the risk function, in that

a1) one selects two sending neurons that are connected to one and the same receiving neuron,

a2) one assumes that the signals output from said sending neurons to the receiving neuron essentially exhibit the same qualitative behavior, that is to say are correlated to one another,

a3) one interrupts the synapse of one of the two sending neurons to the receiving neuron and instead adapts accordingly the weight of the synapse of the respective other sending neuron to the receiving neuron,

a4) one compares the reaction of the neural network changed in accordance with step a3) with the reaction of the unchanged neural network, and

a5) if the variation of the reaction does not exceed a predetermined level, one decides to keep the change made in step a3).

2. The method as claimed in claim 1, characterized in that the two sending neurons are located on one and the same layer.

3. The method as claimed in claim 1 or 2, characterized in that furthermore the value of the bias of the receiving neuron is adapted in step a3).

4. A method for training a neural network in accordance with the preamble of claim 1 and if desired with the characterizing parts of any of claims 1 to 3, characterized in that the training of the neural network comprises a structure simplification procedure, that is to say the location and elimination of synapses that have no significant influence on the curve of the risk function, in that

b1) one selects a synapse,

b2) one assumes that said synapse does not have a significant influence on the curve of the risk function,

b3) one interrupts said synapse,

b4) one compares the reaction of the neural network changed in accordance with step b3) with the reaction of the unchanged neural network, and

b5) if the variation of the reaction does not exceed a predetermined level, one decides to keep the change made in step b3).

5. The method as claimed in claim 4, characterized in that, when in the course of the structure simplification procedure n-1 synapses have already been eliminated and the strength of the influence of an nth synapse is being tested, the reaction of the neural network reduced by n synapses is not only compared with the reaction of a network reduced by only n-1 synapses, but also with the reaction of the neural network with its complete structure as present at the beginning of said structure simplification procedure, and in that the

elimination of the nth synapse is only retained if the deviation of the reaction does not exceed a predetermined level for both comparisons.

6. The method as claimed in any of claims 1 to 5, characterized in that the value of a likelihood function is calculated for the neural network to represent the reaction of the neural network.

7. The method as claimed in any of claims 1 to 6, characterized in that the structure variants of the neural network are compared using a significance test.

8. The method as claimed in claim 7, characterized in that the structure variants of the neural network are compared using the CHI-SQUARED test which is known per se.

9. The method as claimed in claim 7, characterized in that the structure variants of the neural network are compared using the BOOT-STRAPPING method which is known per se.

10. The method as claimed in any of claims 1 to 8, characterized in that, to compare two structure variants of the neural network, the ratio of the values of the likelihood functions for said two structure variants is calculated.

11. A method for training a neural network in accordance with the preamble of claim 1 and if desired with the characterizing parts of any of claims 1 to 10, characterized in that the training of the neural network comprises an optimization procedure in which the strengths of the individual synapses, that is to say the strengths of the connections between the neurons, are optimized, and in that the simplex method which is known per se is used for said optimization.

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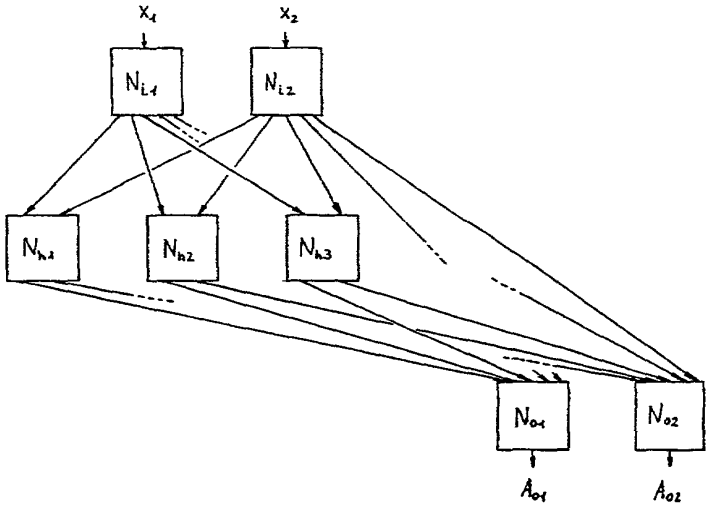
[Fortsetzung auf der nächsten Seite]

(54) Title: METHOD FOR TRAINING A NEURAL NETWORK

(54) Bezeichnung: VERFAHREN ZUM TRAINIEREN EINES NEURONALEN NETZES



(57) **Abstract:** The object of the inventive method is to train a neural network to determine risk functions in patients in association with a first illness relating to a predetermined illness based on the predetermined training data sets. Said predetermined data sets contain objectifiable information which can be used as a yardstick to measure the pathological condition of the patient. The neural network contains a plurality of neurons arranged in several layers, in addition to synapses connecting said neurons. In the course of the training, the structure of the neural network is simplified by tracking and eliminating the synapses which play no significant role in the evolution of the risk functions. This can be done, for example, by examining a possible correlation between the influences which two sending neurons have on the same receiving neuron, and where possible, eliminating one of the two synapses connecting to the receiving neuron.

(57) **Zusammenfassung:** Das erfindungsgemäße Verfahren dient zum Trainieren eines neuronalen Netzes zur Ermittlung von Risikofunktionen für Patienten im Anschluß an eine Ersterkrankung mit einer vorbestimmten Krankheit auf Grundlage vorgegebener Trainings-Datensätze, welche objektivierbare und

[Fortsetzung auf der nächsten Seite]

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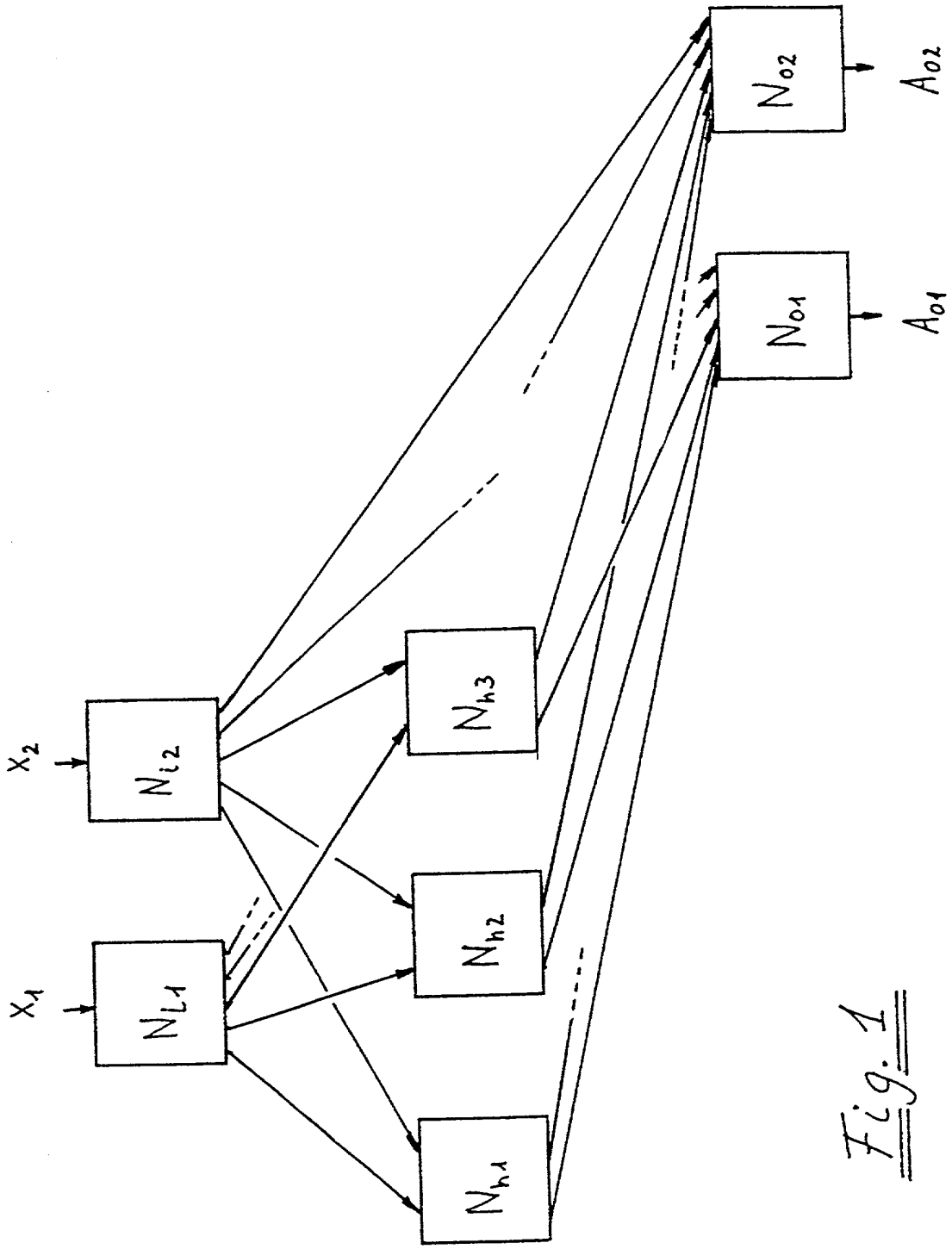

Fig. 1

Docket No. _____ ARENT FOX KINTNER PLOTKIN & KAHN, PLLC
Nikaido, Marmelstein, Murray & Oram Intellectual Property Group

Declaration For U.S. Patent Application

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below my name.
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled
(Insert Title) Method for training a neural network

the specification of which is attached hereto unless the following box is checked:

☒ was filed on 24 August 2000 as PCT International Application
Number PCT/EP00/08280 and was amended on _____
and/or was filed on _____ as United States Application
Number _____ and was amended on _____

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claim(s), as amended by any amendment referred to above.
I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56.
I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate or PCT International Application having a filing date before that of the application(s) for which priority is claimed:

(List prior foreign applications. See Note A on back of this page)	(Number)	(Country)	(Day/Month/Year Filed)	Priority Claimed
	199 40 577.8	Germany	26/August/1999	☒ Yes ☐ No
				☐ Yes ☐ No
				☐ Yes ☐ No

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

(Application Number) (Filing Date)

(Application Number) (Filing Date)

(See Note B on back of this page) ☐ See attached list for additional prior foreign or provisional applications.

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s) or §365(c) of any PCT international application(s) designating the United States of America listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior application(s) (U.S. or PCT) in the manner provided by the first paragraph of 35, U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

(List prior U.S. Applications or PCT International applications designating the U.S.)	(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
	(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

14 — And I hereby appoint as principal attorneys: Robert E. Murray, Reg. No. 22,980; Charles M. Marmelstein, Reg. No. 25,895; George E. Oram, Jr., Reg. No. 27,931; Douglas H. Goldhush, Reg. No. 33,125; David T. Nikaido, Reg. No. 22,663; Monica Chin Kitts, Reg. No. 36,105; Richard J. Berman, Reg. No. 39,107; King L. Wong, Reg. No. 37,500; James A. Poulos, III, Reg. No. 31,714; Patrick D. Muir, Reg. No. 37,403; Murat Ozgu, Reg. No. 44,275; Bradley D. Goldizen, Reg. No. 43,637, N. Alexander Nolte, Reg. No. 45,689 and Robert K. Carpenter, Reg. No. 34,794.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-02 (See Note C on back of this page)

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Inventor's signature Ronald Kates 19 April 2002
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2-0 Full name of second joint inventor, if any Nadia Harbeck

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3-0 Full name of third joint inventor, if any Manfred Schmitt

Inventor's signature _____ Date 22.09.02

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Full name of fourth joint inventor, if any _____

Inventor's signature _____ Date

Residence _____

Citizenship _____

Post Office Address _____

Full name of fifth joint inventor, if any _____

Inventor's signature _____ Date

Residence _____

Citizenship _____

Post Office Address _____

Full name of sixth joint inventor, if any _____

Inventor's signature _____ Date

Residence _____

Citizenship _____

Post Office Address _____

Full name of seventh joint inventor, if any _____

Inventor's signature _____ Date

Residence _____

Citizenship _____

Post Office Address _____

Full name of eighth joint inventor, if any _____

Inventor's signature _____ Date

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Full name of ninth joint inventor, if any _____

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